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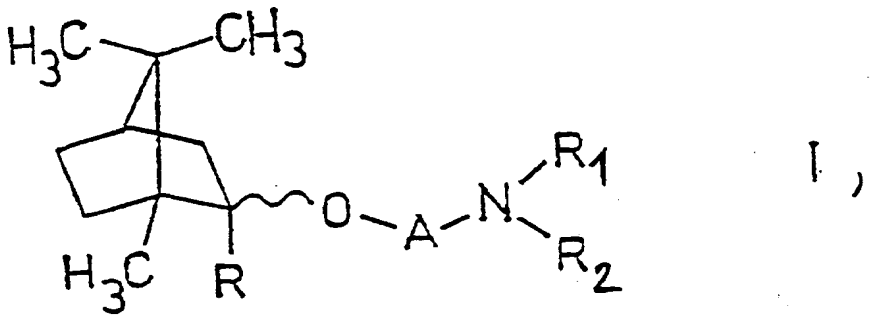
(54) The use of(a) bicycloheptane derivative(s)

(57) The subject matter of the invention is the use of [a] bicycloheptane derivative(s) of formula



I ,

wherein

R	represents a phenyl or a benzyl group,
R_1 and R_2 ,	which may be the same or different stand for straight or branched chained alkyl groups or one of R_1 and R_2 is hydrogen and the other is a straight or branched chained alkyl group,
A	denotes a straight or branched chained alkylene group and
~	represents a valence bond,

and [an] N-oxide(s) as well as [an] optical isomer(s) thereof and mixtures of the optical isomers and [an] acid addition salt(s) and quaternary ammonium derivative(s) of the bicycloheptane derivatives of formula I as well as [an] optical

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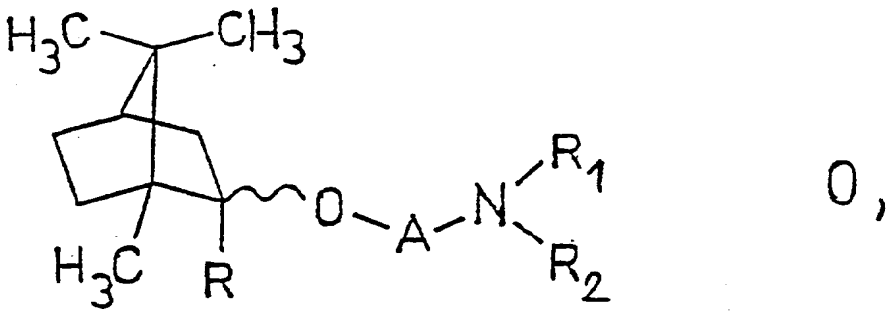
isomer(s) thereof and mixtures of the optical isomers for preparing medicaments for the treatment of diseases and disorders which are connected with the influence on the peripheral cholecystokinin (CCK) system.

Description

The invention concerns a novel medical use of [a] bicycloheptane derivative(s).

It is known that bicycloheptane derivatives of general formula



wherein

R_1 and R_2,	which may be the same or different, represent C_{1-5} alkyl groups or C_{3-6} cycloalkyl groups or they form together with the nitrogen atom to which they are attached a heterocyclic ring containing 4 to 7 carbon atoms and optionally a further hetero atom, e.g. an oxygen, sulfur or nitrogen atom, this latter optionally being substituted by a C_{1-3} alkyl, benzyl or phenyl group,
R	means a phenyl, phenyl-(C_{1-3} alkyl) or thienyl group, optionally substituted by one or are halogen or C_{1-3} alkoxy substituent(s),
A	represents a C_{2-5} straight or branched alkylene chain and
~	represents a valence bond of β configuration,

have anticonvulsive, motility inhibiting and analgesic activities and furthermore potentiate the narcosis induced by 5-(1'-cyclohexenyl)-1,5-di-(methyl)-barbituric acid [hexobarbital]. In case of certain compounds, the above main activities are supplemented by weak antiserotonin, gastrointestinal peristaltic inhibiting and antiinflammatory effects (US-P 4,342,762).

The spastic contraction of the cholecyst occurs, in most instances, if in the gallbladder there are gallstones blocking the bile duct. In case of obstruction, the biliary flow is reduced or stopped, the consequence of which is an elevated pressure in the gallbladder leading to a very strong pain.

Cholelithiasis is a disease that occurs frequently, about 10% of the population is affected by it (W. C. Bowman and M. J. Rand, Textbook of Pharmacology, Blackwell Scientific Publications, Oxford, 1980, p. 2 610). Three main types of gallstones are distinguished in the literature: gallstones of cholesterol type, pigment type and mixed type. The gallstones of mixed type occur most often. In case of women, the occurence of gallstones is twice so high than in case of men. Also in persons having overweight, the occurence of gallstones is are frequent.

In cholelithiasis, the chemotherapy of spastic states is not settled at present since the available drugs do not inhibit the spastic contraction of gallbladder in a selective way.

In general, the surgical intervention (i.e. the removal of the gallstone or cholecyst) is preferred. Chemotherapy includes the administration of nitroglycerol, atropin, analgesics and spasmolytics (J. Knoll, Gyógyszertan, Medicina, Budapest, 1983, p. 372; I. Magyar, Rövid belgyógyászat, Medicina, Budapest, 1985, p. 554; Goodman and Gilman's, The pharmacological basis of therapeutics, Macmillan, New York, 1985, p. 822).

Because of their extremely wide spectrum of effect, atropin and nitroglycerol are rarely employed in practice since a great number of other effects (i.e. side effects) occur, too.

Hence the problem underlying to the invention is to create a novel use of known compounds for preparing superior medicaments for the treatment of diseases and disorders which are connected with the influence on the peripheral cholecystokinin (CCK) system, particularly the spastic contraction of gallbladder, such as bilious attack and biliary colic, which have reduced harmful side effects.

Surprisingly the above problem has been solved by the recognition on which the invention is based as well as by bringing it into practice.

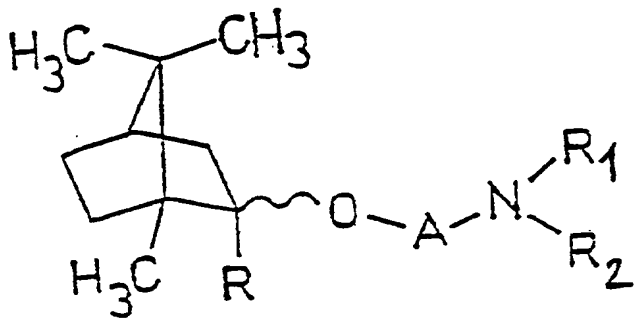
The invention is based on the recognition that bicycloheptane derivatives exert their effect through the inhibition of the peripheral cholecystokinin (CCK) system.

Cholecystokinin is released from the secretory cells being at the distal part of duodenum in the mucosa. In the first place, the release of cholecystokinin is caused by the presence of lipids and essential amino acids. Due to the blood circulation, cholecystokinin reaches the cholecyst giving rise to the contraction thereof, thus, the discharge of bile is realized. Relying upon the results of investigations performed on human beings, it seems that, under physiological conditions, CCK is responsible for the discharge of the gallbladder in 80%.

Thus, if the effect of CCK that releases as a consequence of a physiological stimulus can be blocked, then the contraction of the gallbladder can be prevented - and this is the arm in the present case. In fact, bilious attack can be considered as an extreme contraction (W. C. Bowman and M. J. Rand, Textbook of Pharmacology, Blackwell Scientific Publications, Oxford, 1980, pp. 2 520 to 2 521) that is prevented by the receptor antagonists CCK_A (Beglinget et al., Lancet, Vol. 334, No. 8 655, 1989, p. 167).

Surprisingly, it has been found that the compounds defined as follows inhibit the CCK system.

Hence the subject matter of the invention is the use of [a] bicycloheptane derivative(s) of formula



I ,

wherein

R	represents a phenyl or a benzyl group,
R_1 and R_2 ,	which may be the same or different stand for straight of branched chained alkyl groups having from 1 to 4 carbon atom(s) or one of R_1 and R_2 is hydrogen and the other is a straight or branched chained alkyl group having from 1 to 4 carbon atoms(s),
A	denotes a straight or branched chained alkylene group having from 2 to 4 carbon atoms and
~	represents a valence bond,

and [an] N-oxide(s) as well as [an] optical isomer(s) thereof and mixtures of the optical isomers and [an] acid addition salt(s) and quaternary ammonium derivative(s) of the bicycloheptane derivatives of formula I as well as [an] optical isomer(s) thereof and mixtures of the optical isomers for preparing medicaments for the treatment of diseases and disorders which are connected with the influence on the peripheral cholecystokinin (CCK) system.

Preferably the use according to the invention is for preparing medicaments preventing the spastic contraction of the gallbladder.

The use according to the invention has the therapeutical advantage that it is able to influence, in a selective manner, the system being in direct connection with the gallbladder, thus, in addition to enhancing the efficaciousness of the therapy, the probability of the appearance of harmful side effects is reduced.

Examples for alkyl groups having from 1 to 4 carbon atoms are methyl, ethyl, n-propyl and isopropyl groups.

It is preferred that as bicycloheptane derivative(s) such in which the alkyl group(s) which is/are represented by R_1 and/or R_2 has/have 1 or 2, particularly 1, carbon atom(s) is/are employed. Above all in case that R_1 and R_2 both stand for alkyl groups they represent ethyl groups.

Furthermore it is preferred that as bicycloheptane derivative(s) such in which the alkylene group represented by A has 2 or 3, particularly 2, carbon atoms is/are employed. Most preferably A stands for an ethylene, propylene or 2-(methyl)-propylene group.

Formula I of the bicycloheptane derivatives used according to the invention includes all possible optical isomers und any mixtures thereof. The bicycloheptane derivatives of general formula I can correspond to configurations (1R,2S,4R), (1S,2R,4S) or (1RS,2RS,4RS); a preferred configuration is (1R,2S,4R).

Suitably the acid addition salts of the bicycloheptane derivatives of general formula I are pharmaceutically acceptable ones. They can have been formed with inorganic acids, e.g. hydrohalogenic acids, such as hydrochloric acid or hydrobromic acid, sulfuric acid, phosphoric acid or nitric acid, or organic acids, e.g. tartaric acid, succinic acid, malic acid,

maleic acid, fumaric acid, citric acid, lactic acid, methanesulfonic acid or p-toluenesulfonic acid those with fumaric acid being preferred.

The quaternary ammonium derivatives of the bicycloheptane derivatives of general formula I can have been formed by reacting the bicycloheptane derivatives of general formula I with alkyl halides, e.g. methyl, ethyl, n-propyl or isopropyl chloride, bromide or iodide.

It is especially preferred that as bicycloheptane derivative(s) (1R,2S,4R)-(-)-2-[phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane and/or [an] acid addition salt(s), particularly (1R,2S,4R)-(-)-2-[phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane (E)-2-butenedioate (salt of the former with fumaric acid), is/are employed since these compounds have particularly useful pharmacological properties.

It is also preferred that as bicycloheptane derivative(s) (1R,2S,4R)-(-)-2-[benzyl]-2-[3'-(dimethylamino)-propoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane, (1R,2S,4R)-(-)-2-[benzyl]-2-[2'-(methyl)-3'-(dimethylamino)-propoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane, (1RS,2RS,4RS)-2-[phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane and/or (1S,2R,4S)-(+)-2-[phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane and/or [an] acid addition salt(s), particularly the (E)-2-butenedioate(s), thereof is/are employed.

Conveniently the use according to the invention is for preparing as medicaments pharmaceutical compositions, particularly for oral, rectal or parenteral administration. Preferably the use according to the invention is for preparing as medicaments pharmaceutical compositions in the form of tablets, enteric-coated tablets, capsules, dragées, solutions, suspensions, suppositories or injectable solutions.

It is also preferred that the use according to the invention is for preparing as medicaments pharmaceutical compositions which contain from 10 to 100 mg of bicycloheptane derivative(s) in an unit dosage. This is particularly true in case of tablets, enteric-coated tablets, dragées and capsules.

These pharmaceutical compositions can be prepared by conventional methods used in the manufacture of pharmaceutical compositions, suitably by admixing the bicycloheptane derivative(s) of general formula I in a manner known in itself to 1 or are conventional solid and/or liquid pharmaceutical carrier(s) and/or auxiliary material(s) and transforming the mixture obtained into a pharmaceutical composition.

Preferably the above solid pharmaceutical compositions prepared by the use according to the invention comprise silica and/or 1 or are binding agent(s), such as poly-(vinylpyrrolidone) and/or gelatin. Furthermore 1 or more lubricant(s), such as magnesium stearate, talc and/or sodium laurylsulfate, can be present additionally to the bicycloheptane derivative(s) in the tablets.

In case of aqueous suspensions and/or elixirs suitable for oral treatment prepared by the use according to the invention, the bicycloheptane derivative(s) can be present in mixture with 1 or more different flavouring agent(s), dyestuff(s), emulgator(s) and/or diluent(s), such as water, ethanol, propylene glycol and/or glycerol.

The tablets prepared by the use according to the invention can be manufactured using dry or wet granulation processes. Dragées can be prepared by coating the core in a usual manner. For the preparation of capsules, the suitable mixture is filled into hard or soft gelatin capsules.

The pharmaceutical compositions prepared by the use according to the invention inhibiting the spastic contraction of the gallbladder are, in general, administered in a dose of 0.25 to 40 mg, preferably 1 to 20 mg, for each kg body weight, in 1 to 3 portions, daily. The actual dosage is determined depending on the activity of the bicycloheptane derivative(s), the method of treatment, the state of the patient and other factors, as described by the attending physician.

The daily dose of the bicycloheptane derivatives used according to the invention depends on the conditions of the given case, e.g. the body weight and age of the patient and the severity of the disorder to be treated, and is determined by the physician. The daily dose for an adult patient is, in general, about 1 mg to about 100 mg of bicycloheptane derivative(s).

The effect of the bicycloheptane derivatives used according to the invention is verified on the following test. Known spasmolytics 1-[3',4'-di-(ethoxy)-benzyliden]-6,7-di-[ethoxy]-1,2,3,4-tetra-[hydro]-isoquinoline {drotaverine} and 1-[3',4'-di-(methoxy)-benzyl)-6,7-di-[methoxy]-isoquinoline {papaverine} are employed for comparison. (These spasmolytics are most often used in the therapeutical practice).

The tests were performed on male mice from the strain NMRI in groups consisting of 8 to 12 animals. At the beginning of the test, the animals were weighing 20 to 30 g.

The animals were starved for 24 hours before beginning the first treatment, however, they were allowed to consume water ad libitum. The compounds to be tested and the carrier (0.4% solution of methyl cellulose) were administered perorally in a volume of 10 ml/kg.

45 minutes after this treatment, an emulsion of 30% of yolk in 0.4% methyl cellulose solution was administered perorally. Each mouse consumed 0.5 ml of the emulsion. The animals of the control group consumed 0.5 ml of the carrier i.e. 0.4% methyl cellulose solution.

After 15 minutes, cervicalis dislocatio was employed, the gallbladders were removed and weighed, one by one. The effect of the compounds tested was given as the inhibition of the cholecyst mass decrease induced by yolk, in percentage. From the effects expressed in percentage, ID_{50} values (i.e. doses causing 50% inhibition) were calculated on the basis of dose versus effect correlations by linear regression (Makovec et. al., Pharm. Res. Com., Vol, 19, No. 1, [1987], p. 41).

The results obtained are summarized in the following table.

Table

Compound tested	ID_{50} p.o. in mg/kg
(1R,2S,4R)-(-)-2-[Phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane (E)-2-butenedioate	7.0
(1S,2R,4S)-(+)-2-[Phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane (E)-2-butenedioate	higher than 100
(1RS,2RS,4RS)-2-[Phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane (E)-2-butenedioate	10 to 100
(1R,2S,4R)-(-)-2-[Phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane-N-oxide (E)-2-butenedioate	higher than 100
(1R,2S,4R)-(-)-2-[Phenyl]-2-[2'-(methylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane (E)-2-butenedioate	10 to 100
(1R,2S,4R)-(-)-2-[Benzyl]-2-[2'-(methyl)-3-di-(methylamino)-propoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane (E)-2-butenedioate	10 to 100
(1R,2S,4R)-(-)-2-[Benzyl]-3-[3'-(dimethylamino)-propoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane (E)-2-butenedioate	10 to 100
1-[3',4'-di-(Ethoxy)-benzyliden]-6,7-di-[ethoxy]-1,2,3,4-tetra-[hydro]-isoquinoline {Drotaverine} <Reference substance I>	higher than 100
1-[3',4'-di-(Methoxy)-benzyl]-6,7-di-[methoxy]-isoquinoline {Papaverine} <Reference substance II>	higher than 100

From the above comparison it can be seen that, as to activity, the bicycloheptane derivatives used according to the invention for the most part surpass the known spasmolytics used for comparison and at least reach them. Thus, (1R,2S,4R)-(-)-2-[phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane (E)-2-butenedioate

inhibits the cholecyst contraction induced by yolk at a dose of as low as 7 mg/kg more efficiently by one order of magnitude than the known spasmolytics used for comparison.

Consequently, the pharmaceutical compositions prepared from the bicycloheptane derivatives by the use according to the invention can be effectively employed in clinical patterns which include the CCK system as a pathogen factor, such as the spastic contraction of gallbladder in the first place, furthermore other diseases and disorders, for instance acute pancreatitis.

It is deemed that the spasmolytic mechanism of the bicycloheptane derivatives of general formula I and its derivatives in the treatment of bilious attacks is different from that of the known spasmolytics. Drugs relieving the spastic state of the smooth muscle are called spasmolytics. The smooth muscle spasmolytics, such as 1-[3',4'-di-(methoxy)-benzyl]-6,7-di-[methoxy]-isoquinoline (papaverine) or 1-[3',4'-di-(ethoxy)-benzyliden]-6,7-di-[ethoxy]-1,2,3,4-tetra-[hydro]-isoquinoline (drotaverine), are not able to relieve the spasms of the skeletal muscle.

The bicycloheptane derivatives used according to the invention do not show a direct spasmolytic effect in tests with isolated organs, however, they can relieve the bilious attacks induced experimentally. This contradiction is explained by the fact that the bicycloheptane derivatives used according to the invention influence the CCK system. This effect of these substances is novel and surprising for the expert.

The invention is further elucidated by the following Examples.

Example 1

Tablet containing 25 mg of active ingredient

One tablet contains:

(1R,2S,4R)-(-)-2-[phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane (E)-2-butenedioate	25.0 mg
maize starch	97.0 mg
poly-(vinylpyrrolidone)	75.0 mg
magnesium stearate	3.0 mg
	200.0 mg

Preparation:

A mixture of the active ingredient and maize starch is granulated by wetting with a 15% by weight aqueous poly-(vinylpyrrolidone) solution and drying at 40 to 45°C. The granules are dried again, then mixed with magnesium stearate and tabletted. The weight of a tablet is 200.0 mg.

Example 2

Dragée containing 25 mg of active ingredient

One dragée core contains:

(1R,2S,4R)-(-)-2-[phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane (E)-2-butenedioate	25.0 mg
maize starch	245.0 mg
gelatin	8.0 mg
talc	18.0 mg
magnesium stearate	4.0 mg
	300.0 mg

Preparation:

A mixture of the active ingredient and maize starch is wetted with a 10% aqueous gelatin solution, then granulated by passing it through a sieve, and dried at 40 to 45°C. The dry granules are again passed through a sieve, homogenized with talc and magnesium stearate, and compressed to dragée cores weighing 300.0 mg each.

The dragée cores obtained are coated with a layer consisting of sugar and talc in a manner known per se. The dragées obtained are polished with beeswax.

Example 3

Dragée containing 50 mg of active ingredient

One dragée core contains:

(1RS,2RS,4RS)-2-[phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane (E)-2-butenedioate	50.0 mg
lactose	94.0 mg
poly-(vinylpyrrolidone)	4.0 mg
magnesium stearate	2.0 mg
	150.0 mg

Preparation:

The granules and dragée cores are prepared as described in Example 2. The weight of a dragée core is 150.0 mg. Then, the cores are coated as given in Example 2 to obtain dragées.

Example 4

Gelatin capsule containing 25 mg of active ingredient

One capsule contains:

(1R,2S,4R)-(-)-2-[phenyl]-2-[2'-(methylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane (E)-2-butenedioate	25.0 mg
maize starch	265.0 mg
silicium dioxide [Aerosil®]	6.0 mg
magnesium stearate	4.0 mg
	300.0 mg

Preparation:

The ingredients are homogenized, then filled into gelatin capsules of suitable size.

Example 5

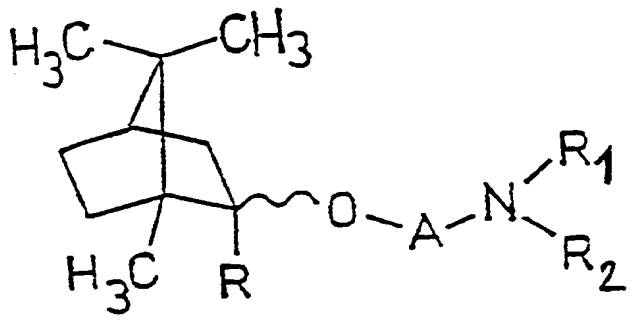
Injectable solution containing 25 mg of (1R,2S,4R)-(-)-2-[phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane (E)-2-butenedioate

One ampoule contains:

active ingredient of formula I	25.0 mg
in 1 ml of water which was distilled twice.	

Claims

1. The use of [a] bicycloheptane derivative(s) of formula



I ,

wherein

R	represents a phenyl or a benzyl group,
R_1 and R_2 ,	which my be the same or different stand for straight or branched chained alkyl groups having from 1 to 4 carbon atoms(s) or one of R_1 and R_2 is hydrogen and the other is a straight or branched chained alkyl group having from 1 to 4 carbon atom(s),
A	denotes a straight or branched chained alkylene group having from 2 to 4 carbon atoms and
~	represents a valence bond,

and [an] N-oxide(s) as well as [an] optical isomer(s) thereof and mixtures of the optical isomers and [an] acid addition salt(s) and quaternary ammonium derivative(s) of the bicycloheptane derivatives of formula I as well as [an] optical isomer(s) thereof and mixtures of the optical isomers for preparing medicaments for the treatment of diseases and disorders which are connected with the influence on the peripheral cholecystokinin (CCK) system.

2. The use according to claim 1, characterized in that it is for preparing medicaments preventing the spastic contraction of the gallbladder.

3. The use according to claim 1 or 2, characterized in that as bicycloheptane derivative(s) such in which the alkyl group(s) which is/are represented by R_1 and/or R_2 has/have 1 or 2 carbon atoms(s) is/are employed.

4. The use according to claims 1 to 3, characterized in that as bicycloheptane derivative(s) such in which the alkylene group represented by A has 2 or 3 carbon atoms is/are employed.

5. The use according to claims 1 to 4, characterized in that as bicycloheptane derivative(s) (1R,2S,4R)-(-)-2-[phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane and/or [an] acid addition salt(s), particularly (1R,2S,4R)-(-)-2-[phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane (E)-2-butenedioate, is/are employed.

6. The use according to claims 1 to 5, characterized in that as bicycloheptane derivative(s) (1R,2S,4R)-(-)-2-[benzyl]-2-[3'-(dimethylamino)-propoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane, (1R,2S,4R)-(-)-2-[benzyl]-2-[2'-(methyl)-3'-(dimethylamino)-propoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane, (1RS,2RS,4RS)-2-[phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane and/or (1S,2R,4S)-(+)-2-[phenyl]-2-[2'-(dimethylamino)-ethoxy]-1,7,7-tri-[methyl]-bicyclo[2.2.1]heptane and/or [an] acid addition salt(s), particularly the (E)-2-butenedioate(s), thereof is/are employed.

7. The use according to claims 1 to 6, characterized in that it is for preparing as medicaments pharmaceutical compositions, particularly for oral, rectal or parenteral administration.

8. The use according to claims 1 to 7, characterized in that it is for preparing as medicaments pharmaceutical compositions in the form of tablets, enteric-coated tablets, capsules, dragées, solutions, suspensions, suppositories or injectable solutions.

9. The use according to claims 1 to 8, characterized in that it is for preparing as medicaments pharmaceutical compositions which contain from 10 to 100 mg of bicycloheptane derivative(s).

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 11 0311

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,A	US-A-4 342 762 (BUDAI ET AL.) 3 August 1982 * the whole document * ---	1-9	A61K31/135
A	ARZNEIM.-FORSCH., vol. 39, no. 3, 1989 pages 295-297, I. KOVACS ET AL. 'INHIBITION OF HIGH-AFFINITY SYNAPTOSOMAL UPTAKE OF gamma-AMINOBUTYRIC ACID BY A BICYCLO-HEPTANE DERIVATIVE' * the whole document * ---	1-9	
A	ANNALES PHARMACEUTIQUES FRANCAISE, vol. 24, no. 3, 1966 pages 185-190, R. BARONNET ET AL. 'ETUDE D'ETHERS OXYDES AMINES D'ALCOOLS TERPENIQUES' * the whole document * ---	1-9	
D,A	THE LANCET, vol. 334, no. 8, 1989 page 167 C. BEGLINDER ET AL. 'TREATMENT OF BILIARY COLIC WITH LOXIGLUMIDE' * the whole document * -----	1-9	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	28 September 1995	Hoff, P

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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